NDA 22-427

ACUVAIL (ketorolac tromethamine ophthalmic solution)
0.45% Preservative-Free

Allergan, Inc.

Lin Qi
Division of Anti-Infective and Ophthalmology Product
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1. NDA 22-427

2. REVIEW #: 2

3. REVIEW DATE: 7/14/09

4. REVIEWER: Lin Qi

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7. NAME & ADDRESS OF APPLICANT:

   Name: Allergan, Inc.
   Address: 2525 Dupont Drive
             Irvine, CA 92612
   Representative: Elizabeth Bancroft
8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: ACUVAIL
   b) Non-Proprietary Name (USAN): Ketotolac tromethamine
   c) Code Name/# (ONDC only): N/A
   d) Chem. Type/Submission Priority (ONDC only):
      • Chem. Type: 3
      • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: For the treatment of pain and inflammation following cataract surgery

11. DOSAGE FORM: Ophthalmic solution

12. STRENGTH/POTENCY: 0.45%

13. ROUTE OF ADMINISTRATION: Topical, ophthalmic

14. Rx/OTC DISPENSED: __Rx __OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed
    ___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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1 Action codes for DMF Table:
1 – DMF Reviewed.
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

2 Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:
The Chemistry Review for NDA 22-427

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for approval based on product quality assessment.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance ketorolac tromethamine is a white to off-white crystalline powder with a pKa of 3.49. It is a tromethamine [HOCH₂CNH₂(CH₃OH)₂] salt of ketorolac in a 1 to 1 molar ratio. The drug substance is freely soluble in water (>100 mg/mL) at room temperature and pH 6.8. Ketorolac tromethamine is manufactured at ACULAR, NDA 21-528 and is utilized for the current marketed product.

The proposed drug product, ketorolac tromethamine ophthalmic solution 0.45%, is a sterile, non-preserved, clear, and colorless to pale yellow isotonic ophthalmic solution. This formulation contains 0.45% (w/v) ketorolac tromethamine. The inactive ingredients include carboxymethylcellulose, sodium chloride, and sodium citrate. The pH of the bulk solution is adjusted using either 1N sodium hydroxide or 1N hydrochloric acid to a target pH of 6.8 for the final product. The drug product is packaged in clear, LDPE, unit dose vials in a 0.4 mL nominal fill volume/0.9 mL fill capacity. The drug product will be manufactured at Allergan America, Waco, Tx.

B. Description of How the Drug Product is Intended to be Used

The proposed indication is for the treatment of pain and inflammation following cataract surgery. One drop of the drug product should be applied by the patient to the affected eye twice daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. A total of 4 drops should be administered the day of cataract surgery by medical personnel. The 30 vials supply can be used for the whole treatment period according the proposed dosing regimen.
C. Basis for Approvability or Not-Approval Recommendation

The remaining issues from CMC review #1 dated April 30, 2009 relate to microbiological product quality and the GMP status of the additional endotoxin testing sites.

Dr. Bryan recommended approval in his product quality microbiological review dated July 2, 2009.

The applicant stated that the additional endotoxin testing facility, Allergan, Inc., Pharmaceutical Analysis (PAM) does not perform endotoxin testing on the finished product. The only test conducted by this facility is an endotoxin test for one of the excipients (b)(4). Therefore, this facility does not need to be inspected. The overall recommendation on GMP status of facilities recommended by the Office of Compliance is “Acceptable”.

III. Administrative

A. Reviewer's Signature

{Signed and dated electronically in DFS}

B. Endorsement Block

{Signed and dated electronically in DFS}

C. CC Block

Pharmaceutical Assessment Lead
Project Manager

7 Pages Withheld as b(4) Trade Secret/Confidential
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
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Lin Qi
7/15/2009 10:56:15 AM
CHEMIST

Norman Schmuff
7/15/2009 01:01:02 PM
CHEMIST
NDA 22-427

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1. NDA 22-427

2. REVIEW #: 1

3. REVIEW DATE: 4/30/2009

4. REVIEWER: Lin Qi

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   Name: Allergan, Inc.
   Address: 2525 Dupont Drive
             Irvine, CA 92612
   Representative: Elizabeth Bancroft
   Telephone: 714-246-4391
8. DRUG PRODUCT NAME/CODE/TYPEx:
   
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   • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

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19. **ORDER OF REVIEW** (ODG Only)

The application submission(s) covered by this review was taken in the date order of receipt.  ____ Yes  ____ No  If no, explain reason(s) below:
The Chemistry Review for NDA 22-427

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not recommended for approval as there are pending issues related to adequate acceptance criteria for drug product endotoxin testing. All other drug product quality (CMC) issues are satisfactory, including the GMP status of facilities which the Office of Compliance recommends as "Acceptable".

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance ketorolac tromethamine is a white to off-white crystalline powder with a pKa of 3.49. It is a tromethamine [HOCH2CNH2(CH2OH)2] salt of ketorolac in a 1 to 1 molar ratio. The drug substance is freely soluble in water (>100 mg/mL) at room temperature and pH 6.8. KETOROLAC TROMETHAMINE is utilized for the current marketed product ACULAR, NDA 21-528.

The proposed drug product, ketorolac tromethamine ophthalmic solution 0.45%, is a sterile, non-preserved, clear, and colorless to pale yellow isotonic ophthalmic solution. This formulation contains 0.45% (w/v) ketorolac tromethamine. The inactive ingredients include carboxymethylcellulose (b) (4), sodium chloride (b) (4), and sodium citrate (b) (4). The pH of the bulk solution is adjusted using either 1N sodium hydroxide or 1N hydrochloric acid to a target pH of 6.8 for the final product. The drug product is packaged in clear, LDPE, unit dose vials in a 0.4 mL nominal fill volume/0.9 mL fill capacity. The drug product will be manufactured at Allergan America, Waco, Tx.

B. Description of How the Drug Product is Intended to be Used

The proposed indication is for the treatment of pain and inflammation following cataract surgery. One drop of the drug product should be applied by the patient to the affected eye twice daily beginning 1 day prior to cataract surgery, continued on the day of surgery...
and through the first 2 weeks of the postoperative period. A total of 4 drops should be administered the day of cataract surgery by medical personnel.

C. Basis for Approvability or Not-Approval Recommendation

The active drug substance ketorolac tromethamine is utilized in an approved drug product under NDA 21-528 (Acular). The purpose of current application is to develop a non-preserved ophthalmic formulation of ketorolac which offers an effective treatment without the possibility of preservative toxicity.

Appropriate information are provided regarding manufacturing process, process controls, and product controls. Based on the statistical evaluation on 12 months of long term stability potency data and 18 months of long term stability data from the supportive lot, the projected expiration date is greater than 36 months for both the primary stability batches and the supportive stability batch. The proposed expiration dating for the ketorolac tromethamine ophthalmic solution 0.45% is 24 months for market configuration and the physician sample configuration when stored at 15° - 30°C (59° - 86°F) protect from light. This expiry period is acceptable.

In the amendment dated November 21, 2009, the applicant committed to establishing a drug product endotoxin specification by April 30, 2009. This application is recommended for approval pending adequate acceptance criteria for drug product endotoxin testing and a satisfactory quality microbiological review.

III. Administrative

A. Reviewer’s Signature

{Signed and dated electronically in DFS}

B. Endorsement Block

{Signed and dated electronically in DFS}

C. CC Block

Pharmaceutical Assessment Lead
Project Manager